Holt-Oram syndrome

Holt-Oram syndrome is characterized by skeletal abnormalities of the hands and arms (upper limbs) and heart problems.

People with Holt-Oram syndrome have abnormally developed bones in their upper limbs. At least one abnormality in the bones of the wrist (carpal bones) is present in affected individuals. Often, these wrist bone abnormalities can be detected only by x-ray. Individuals with Holt-Oram syndrome may have additional bone abnormalities including a missing thumb, a long thumb that looks like a finger, partial or complete absence of bones in the forearm, an underdeveloped bone of the upper arm, and abnormalities of the collar bone or shoulder blades. These skeletal abnormalities may affect one or both of the upper limbs. If both upper limbs are affected, the bone abnormalities can be the same or different on each side. In cases where the skeletal abnormalities are not the same on both sides of the body, the left side is usually more severely affected than the right side.

About 75 percent of individuals with Holt-Oram syndrome have heart (cardiac) problems, which can be life-threatening. The most common problem is a defect in the muscular wall (septum) that separates the right and left sides of the heart. A hole in the septum between the upper chambers of the heart (atria) is called an atrial septal defect (ASD), and a hole in the septum between the lower chambers of the heart (ventricles) is called a ventricular septal defect (VSD). Some people with Holt-Oram syndrome have cardiac conduction disease, which is caused by abnormalities in the electrical system that coordinates contractions of the heart chambers. Cardiac conduction disease can lead to problems such as a slower-than-normal heart rate (bradycardia) or a rapid and uncoordinated contraction of the heart muscle (fibrillation). Cardiac conduction disease can occur along with other heart defects (such as ASD or VSD) or as the only heart problem in people with Holt-Oram syndrome.

The features of Holt-Oram syndrome are similar to those of a condition called Duane-radial ray syndrome; however, these two disorders are caused by mutations in different genes.

Frequency

Holt-Oram syndrome is estimated to affect 1 in 100,000 individuals.

Genetic Changes

Mutations in the *TBX5* gene cause Holt-Oram syndrome. This gene provides instructions for making a protein that plays a role in the development of the heart and upper limbs before birth. In particular, this gene appears to be important for the process

that divides the developing heart into four chambers (cardiac septation). The *TBX5* gene also appears to play a critical role in regulating the development of bones in the arm and hand. Mutations in this gene probably disrupt the development of the heart and upper limbs, leading to the characteristic features of Holt-Oram syndrome.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Other Names for This Condition

- atrio-digital syndrome
- atriodigital dysplasia
- cardiac-limb syndrome
- heart-hand syndrome, type 1
- HOS
- ventriculo-radial syndrome

Diagnosis & Management

These resources address the diagnosis or management of Holt-Oram syndrome:

- GeneReview: Holt-Oram Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1111
- Genetic Testing Registry: Holt-Oram syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265264/
- MedlinePlus Encyclopedia: Atrial Septal Defect
  https://medlineplus.gov/ency/article/000157.htm
- MedlinePlus Encyclopedia: Skeletal Limb Abnormalities
  https://medlineplus.gov/ency/article/003170.htm
- MedlinePlus Encyclopedia: Ventricular Septal Defect
  https://medlineplus.gov/ency/article/001099.htm

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html

- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Atrial Septal Defect
  https://medlineplus.gov/ency/article/000157.htm
- Encyclopedia: Skeletal Limb Abnormalities
  https://medlineplus.gov/ency/article/003170.htm
- Encyclopedia: Ventricular Septal Defect
  https://medlineplus.gov/ency/article/001099.htm
- Health Topic: Congenital Heart Defects
  https://medlineplus.gov/congenitalheartdefects.html
- Health Topic: Hand Injuries and Disorders
  https://medlineplus.gov/handinjuriesanddisorders.html

Genetic and Rare Diseases Information Center

- Holt-Oram syndrome
  https://rarediseases.info.nih.gov/diseases/6666/holt-oram-syndrome

Additional NIH Resources

- National Heart, Lung, and Blood Institute: What Are Holes in the Heart?
  https://www.nhlbi.nih.gov/health/health-topics/topics/holes/

Educational Resources

- American Heart Association: Common Types of Heart Defects
  http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/AboutCongenitalHeartDefects/Common-Types-of-Heart-Defects_UCM_307017_Article.jsp
- Disease InfoSearch: Holt-Oram syndrome
  http://www.diseaseinfosearch.org/Holt-Oram+syndrome/3457
- MalaCards: holt-oram syndrome
  http://www.malacards.org/card/holt_oram_syndrome

- March of Dimes: Congenital Heart Defects
  http://www.marchofdimes.org/baby/congenital-heart-defects.aspx
- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Holt-Oram%20syndrome&type=profile
- Nemours Foundation: Congenital Heart Defects
  http://kidshealth.org/en/parents/if-heart-defect.html
- Orphanet: Holt-Oram syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=392

Patient Support and Advocacy Resources

- American Society for Surgery of the Hand
  http://www.assh.org/handcare/hand-arm-conditions/Congenital-Differences
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/holt-oram-syndrome/
- Resource List from the University of Kansas Medical Center: Heart Conditions
  http://www.kumc.edu/gec/support/conghart.html
- Resource List from the University of Kansas Medical Center: Limb Anomalies
  http://www.kumc.edu/gec/support/limb.html

GeneReviews

- Holt-Oram Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1111

Genetic Testing Registry

- Holt-Oram syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265264/

Scientific articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Abnormalities,+Multiple%5BMAJR%5D%29+AND+%28holt-oram+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- HOLT-ORAM SYNDROME
  http://omim.org/entry/142900

Sources for This Summary

- Basson CT, Cowley GS, Solomon SD, Weissman B, Poznanski AK, Traill TA, Seidman JG, Seidman CE. The clinical and genetic spectrum of the Holt-Oram syndrome (heart-hand syndrome). N Engl J Med. 1994 Mar 31;330(13):885-91. Erratum in: N Engl J Med 1994 Jun 2;330(22):1627.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8114858
- Boogerd CJ, Dooijes D, Ilgun A, Mathijssen IB, Hordijk R, van de Laar IM, Rump P, Veenstra-Knol HE, Moorman AF, Barnett P, Postma AV. Functional analysis of novel TBX5 T-box mutations associated with Holt-Oram syndrome. Cardiovasc Res. 2010 Oct 1;88(1):130-9. doi: 10.1093/cvr/cvq178. Epub 2010 Jun 2. Erratum in: Cardiovasc Res. 2011 Jan 1;89(1):253. Mathijssen, Inge B [added].
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20519243
- Cerbai E, Sartiani L. Holt-oram syndrome and atrial fibrillation: opening the (T)-box. Circ Res. 2008 Jun 6;102(11):1304-6. doi: 10.1161/CIRCRESAHA.108.178079.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18535267
- Chryssostomidis G, Kanakis M, Fotiadou V, Laskari C, Kousi T, Apostolidis C, Azariadis P, Chatzis A. Diversity of congenital cardiac defects and skeletal deformities associated with the Holt-Oram syndrome. Int J Surg Case Rep. 2014;5(7):389-92. doi: 10.1016/j.ijscr.2014.04.034. Epub 2014 May 9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24879328
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4064427/
- Debeer P, Race V, Gewillig M, Devriendt K, Frijns JP. Novel TBX5 mutations in patients with Holt-Oram syndrome. Clin Orthop Relat Res. 2007 Sep;462:20-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17534187
- GeneReview: Holt-Oram Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1111
- OMIM: HOLT-ORAM SYNDROME
  http://omim.org/entry/142900
- Hatcher CJ, McDermott DA. Using the TBX5 transcription factor to grow and sculpt the heart. Am J Med Genet A. 2006 Jul 1;140(13):1414-8. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16691575
- Huang T, Lock JE, Marshall AC, Basson C, Seidman JG, Seidman CE. Causes of clinical diversity in human TBX5 mutations. Cold Spring Harb Symp Quant Biol. 2002;67:115-20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12858531
- McDermott DA, Bressan MC, He J, Lee JS, Aftimos S, Brueckner M, Gilbert F, Graham GE, Hannibal MC, Innis JW, Pierpont ME, Raas-Rothschild A, Shanske AL, Smith WE, Spencer RH, St John-Sutton MG, van Maldergem L, Waggoner DJ, Weber M, Basson CT. TBX5 genetic testing validates strict clinical criteria for Holt-Oram syndrome. Pediatr Res. 2005 Nov;58(5):981-6. Epub 2005 Sep 23.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16183809
- Mori AD, Bruneau BG. TBX5 mutations and congenital heart disease: Holt-Oram syndrome revealed. Curr Opin Cardiol. 2004 May;19(3):211-5. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15096952

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